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Short Communication

Novel Findings on EGFR Exon 7 Mutations in Non-Small Cell Lung Cancer (NSCLC): A Clinical and Pathological Analysis of Four Cases

Ana Goás[1], María José Cardiel[2], Sebastián Menao[3], María Arruebo[3], Dolores Isla[1] and Rodrigo Lastra[1]*

[1]Medical Oncology Department, Hospital Clínico Universitario Lozano Blesa, Spain

[2]Patological Department, Hospital Clínico Universitario Lozano Blesa, Spain

[3]Biochemistry-Genetics Department, Hospital Clínico Universitario Lozano Blesa, Spain

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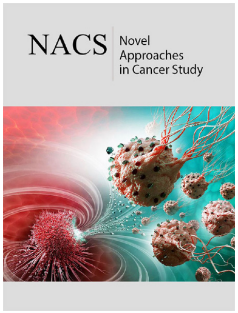

***Corresponding author:** Rodrigo Lastra, Medical Oncology Department, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

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Abstract

Exons 18-21 of the EGFR gene are frequently mutated in NSCLC, often showing favorable responses to TKIs. However, rare EGFR mutations, such as those occurring in exon 7, remain underexplored. This study reports four NSCLC cases with uncommon exon 7 mutations identified via NGS. Three potentially pathogenic variants (c.866C>T, p.A289V; c.866C>A, p.A289D) and two variants of uncertain significance were detected. Among these, one patient who received TKI therapy exhibited early disease progression. Additionally, our patient sample displayed unusual clinical and pathological characteristics, differing from those typically associated with common EGFR mutations. These findings underscore the need for further research into the clinical implications and therapeutic strategies for rare EGFR mutations.

Keywords: Squamous cell; Chemo-radiotherapy; Clinical and pathological; Next-generation sequencing (NGS) and Lung cancer

Introduction

Exons 18 to 21 of the Epidermal Growth Factor Receptor (EGFR) gene are the most frequently mutated regions in patients with NSCLC [1]. Several clinical trials have demonstrated good responses to treatment with Tyrosine Kinase Inhibitors (TKIs) in NSCLC patients with specific EGFR mutations in those exones, such as 19-Del, L858R, T790M, 20-Ins, G719X, S768I, and L861Q [2]. In recent years, the development and standardized implementation of massive parallel sequencing techniques in clinical practice have enabled the identification of rarer mutations, including those in exon 7 of EGFR. In 2018, Dai L et al. [3] reported the c.866C>T (p. A289V) mutation, which affects the extracellular region of EGFR's exon 7. This mutation has not yet been included in major international databases, such as OncoKB, Uncommon EGFR, and ClinVar [4].

Previous studies suggest that this point mutation may disrupt EGFR's normal function and could represent a potential therapeutic target for TKI treatment. However, it has been described mainly in glioblastoma cell lines and rarely in NSCLC cases, with no evidence of TKI treatment effects in NSCLC with the c.866C>T mutation. Nonetheless, the limited documentation regarding EGFR exon 7 mutations in the literature leads to uncertainty about their potential therapeutic response to TKIs and clinical implications. This study describes four cases of NSCLC with rare exon 7 mutations, founded in our healthcare area, providing novel information on their potential clinical and therapeutic impact.

Objective

To describe the clinical, pathological, and molecular characteristics of patients in this case series and to report previously undocumented mutations in exon 7 of EGFR that may have clinical relevance.

Methodology

This retrospective descriptive study analyzed the clinical, pathological and molecular characteristics of four NSCLC patients with rare EGFR exon 7 mutations diagnosed between December 2023 and February 2024 in our health care area. Identification of genetic variants was performed by Next-Generation Sequencing (NGS) using the Oncomine Precision Assay on the Genexus platform, with automated DNA and RNA extraction through the Genexus Purification system (all performed at Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain). Therapeutic decisions were individualized and discussed in a multidisciplinary committee, which evaluated the 'actionability' of the variants according to the ESMO-ESCAT scale recommendations [5], establishing the level of evidence and potential response to targeted therapies.

Findings

Our sample included four NSCLC patients (three men and one woman, aged 74-82, mean age 78). All patients had been exposed to tobacco smoke (three former smokers, one active smoker). Histologically, there were three adenocarcinomas and one squamous cell carcinoma. Two patients exhibited high PD-L1 expression (95% and 80%), one had 2% expression, and PD-L1 status was unavailable for one case.

Molecular analysis revealed three potentially pathogenic variants in exon 7 of EGFR (one c.866C>T, p.A289V and two c.866C>T, p.A289D) and two variants of uncertain significance in the c.857-858 region in another patient. One patient (male, 82 years, PD-L1 2%) with the c.866C>A, p.A289D mutation received third-generation TKI treatment (osimertinib 80 mg/day) based on ESMO-ESCAT scale recommendations (evidence level IB). However, disease progression occurred after three treatment cycles. Two patients underwent platinum-based chemo-radiotherapy: one died from cardiogenic shock due to acute myocardial infarction before response evaluation, and the other is awaiting reevaluation. The fourth patient relocated to their native country, leaving their treatment outcome unknown.

Discussion

In this series we describe three uncommon variants in the c.866 region of EGFR exon 7. Experience with these rare mutations is very limited [2]. The clinical and pathological profiles of our patients differ from those typically associated with common EGFR mutations (e.g., women, young age, non-smokers, absent PD-L1 expression). The early progression observed in the patient treated with a TKI suggests that these exon 7 mutations may not be EGFR inhibition-dependent and may present a different clinical and response pattern compared to patients with common EGFR mutations.

Conclusion

The implementation of NGS in clinical practice has allowed the identification of variants that are not yet well documented in international databases, highlighting the need for further studies and international collaboration to better understanding of their therapeutic and prognostic relevance in NSCLC. Further evaluation of these mutations could guide the creation of new therapeutic strategies for patients with rare EGFR mutations.

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